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J Pharm Sci. 2000 Jun;89(6):771-80.

PMID: 10824136 [PubMed - indexed for MEDLINE]

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In vitro percutaneous absorption enhancement of propranolol hydrochloride through porcine epidermis by terpenes/ethanol.

J Control Release. 1999 Dec 6;62(3):359-66.

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Biol Pharm Bull. 1999 Jun;22(6):642-6.

PMID: 10408241 [PubMed - indexed for MEDLINE]

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Effect of linolenic acid/ethanol or limonene/ethanol and iontophoresis on the in vitro percutaneous absorption of LHRH and ultrastructure of human epidermis.

Int J Pharm. 1999 Apr 15;180(2):235-50.

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Enhancement by terpenes of 5-fluorouracil permeation through the stratum corneum: model solvent approach.

J Pharm Pharmacol. 1998 Sep;50(9):955-64.

PMID: 9811155 [PubMed - indexed for MEDLINE]

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Mechanisms of percutaneous absorption of tamoxifen by terpenes: eugenol, D-limonene and menthone.

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Mechanism for enhancement effect of lipid disperse system on percutaneous absorption.

J Pharm Sci. 1996 Jan;85(1):57-64.

PMID: 8926585 [PubMed - indexed for MEDLINE]

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Terpene penetration enhancers in propylene glycol/water co-solvent systems: effectiveness and mechanism of action.

J Pharm Pharmacol. 1995 Dec;47(12A):978-89.

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Wide-angle X-ray diffraction of human stratum corneum: effects of hydration and terpene enhancer treatment.

J Pharm Pharmacol. 1994 Dec;46(12):938-50.

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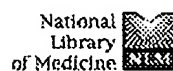
Comparative analysis of percutaneous absorption enhancement by d-limonene and oleic acid based on a skin diffusion model.

Pharm Res. 1994 Mar;11(3):377-83.

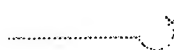
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Cyclic monoterpene extract from cardamom oil as a skin permeation enhancer for indomethacin: in vitro and in vivo studies.

Huang YB, Fang JY, Hung CH, Wu PC, Tsai YH.

School of Pharmacy, Kaohsiung Medical College, Taiwan.

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The in vitro and in vivo effect of pretreatment by cardamom oil, a crude drug extract, in ethanol/water vehicles on the transdermal delivery of indomethacin was investigated. The cyclic monoterpene components in cardamom oil were also determined and quantified in this study. The permeation of indomethacin was significantly enhanced after pretreatment of cardamom oil both in the in vitro and in vivo studies. The result of various pre-treatment periods showed that the indomethacin flux decreased as the length of the pretreatment increased. Both natural cardamom oil and a cyclic monoterpene mixture composed of the components of the oil showed similar enhancement on indomethacin permeation, indicating cyclic monoterpenes are the predominant components altering the barrier property of stratum corneum. The results also showed that three minor components in cardamom oil (alpha-pinene, 6.5%; beta-pinene, 4.8%; alpha-terpineol, 0.4%) had a synergistic effect with 1,8-cineole (59.3%) and d-limonene (29.0%) to enhance the permeation of indomethacin.

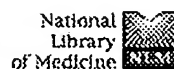
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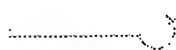
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Liposomal ursolic acid (merotaine) increases ceramides and collagen in human skin.

Yarosh DB, Both D, Brown D.PubMed
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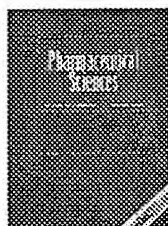
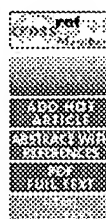
Skin wrinkling and xerosis associated with aging result from decreases of dermal collagen and stratum corneum ceramide content. This study demonstrates that ursolic acid incorporated into liposomes (Merotaine) increases both the ceramide content of cultured normal human epidermal keratinocytes and the collagen content of cultured normal human dermal fibroblasts. In clinical tests, Merotaine increased the ceramide content in human skin over an 11-day period. Merotaine has effects on keratinocyte differentiation and dermal fibroblast collagen synthesis similar to retinoids. However, unlike retinoids, Merotaine increases ceramide content of human keratinocytes. Ursolic acid may bind to members of the glucocorticoid receptor family to initiate changes in keratinocyte gene transcription. Copyright 2001 S. Karger AG, Basel

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Research Article

**Mechanism for enhancement effect of lipid disperse system on
percutaneous absorption**

Taro Ogiso *, Naoko Niinaka, Masahiro Iwaki

Faculty of Pharmaceutical Sciences, Kinki University, Kowakae 3-4-1, Higashi-Osaka, Osaka 577,
Japan.*Correspondence to Taro Ogiso, Faculty of Pharmaceutical Sciences, Kinki University, Kowakae 3-4-1,
Higashi-Osaka, Osaka 577, Japan.**Abstract**

To clarify the mechanism involved in the enhancement effect of lipid disperse systems (LDS) on percutaneous absorption, the effect of the LDSs of betahistine (BH), prepared using egg phosphatidylcholine (EPC, phase transition temperature, T_m , -15 to -17 °C) or hydrogenated soybean phosphatidylcholine (HSPC, T_m , 50 to 60 °C), cholesterol, and dicetylphosphate, on the percutaneous absorption of BH, the amount of skin lipids (ceramides, triglycerides, and phospholipids), the fluidity of skin lipids, and the partitioning of LDS-BH into the skin layers were investigated using Wistar and hairless rats. Also examined was whether the LDS penetrated through the stratum corneum (SC) or follicles, using a fluorescent probe (Nile Red). The plasma concentrations of BH were much higher and more sustained after application of a gel formulation containing EPC-LDS and D-limonene (prep. 2) than those after the non-LDS formulation containing D-limonene (prep. 1), whereas the plasma levels after application of a formulation containing HSPC-LDS (prep. 5) were not largely increased compared with those after prep. 1. The content of ceramides (intercellular lipids) and triglycerides (sebaceous gland lipids) in the SC were dramatically decreased by the treatment with prep. 1 and prep. 2, with the more decreased levels of these lipids by the treatment with prep. 2. The phospholipid content of the SC was enhanced by 2-fold following the prep. 2 treatment, indicating the extensive incorporation of LDS lipids into the SC. The histochemical examination of the skin, following application of EPC-LDS with a fluorescent probe, indicated that the LDS lipids penetrated rapidly through the SC and follicles into the viable skins. The fluidity of the SC lipids was dramatically increased following the treatment with the fluid EPC-LDS, whereas the fluidity was significantly decreased by the solid HSPC-LDS. The BH in each skin layer was also significantly increased by the treatment with prep. 2. These results surely demonstrated that the fluid LDS permeated rapidly into the SC and the viable epidermis through the intercellular domains and the follicles in intact vesicles or lipid mixtures, thus ensuring the facilitated transport of LDS-drug through the skin.

Received: 28 April 1995; Revised: 3 October 1995; Accepted: 4 October 1995

Digital Object Identifier (DOI)

10.1021/js950178x [About DOI](#)

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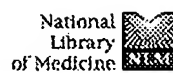
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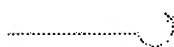
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1: Biol Pharm Bull 1995 Nov;18(11):1566-71

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Percutaneous penetration of fluorescein isothiocyanate-dextrans and the mechanism for enhancement effect of enhancers on the intercellular penetration.

Ogiso T, Paku T, Iwaki M, Tanino T.PubMed
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Faculty of Pharmaceutical Sciences, Kinki University, Osaka, Japan.

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To identify the mechanism involved in the enhancement effect of enhancers on the intercellular penetration of large polar molecules, the skin penetration of fluorescein isothiocyanate (FITC)-dextrans (average molecular weight; 4400, 9400, and 69000 Da) and the lipid removal from the intercellular spaces by enhancers were studied using hairless rat skin. Pretreatment of hairless rat skin with enhancers such as n-octanol (20%), laurocapram (2%), isopropylmyristate (IPM, 20%), oleic acid (5%) and cineol (2%), which are water-immiscible, significantly enhanced the flux of FITC-dextrans, while pretreatment with water-miscible enhancers, i.e. dimethyl sulfoxide (DMSO, 5%) and N-methyl-2-pyrrolidone (NMP) did not increase the flux compared with the control. The penetration of FITC-dextrans was approximately size dependent. n-Octanol, laurocapram, IPM and oleic acid dramatically removed ceramides which are the intercellular lipids, whereas NMP and DMSO partly extracted the sphingolipids. A linear relationship was observed between the flux and removal of ceramides ($p < 0.01$), indicating that the removal of intercellular lipids would cause dramatic dilations between adherent cornified cells and enhance the penetration through the intercellular pathways. When the penetration of FITC-dextrans through Wistar rat skin was compared with that via hairless rat skin, the steady state flux of FITC-dextrans through Wistar rat skin pretreated with water-immiscible enhancers was 1.2- to 4.9-fold higher, suggesting that the penetration of large polar molecules through follicles may play at least some role in the percutaneous absorption.

PMID: 8593481 [PubMed - indexed for MEDLINE]

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L28: Entry 37 of 45

File: USPT

Jul 9, 1996

DOCUMENT-IDENTIFIER: US 5534260 A

TITLE: Percutaneous drug delivery system

Brief Summary Text (17):

Non-enzymatic penetration enhancers, for purposes of this invention, are compositions which enhance the permeation of biologically active agents (e.g. drugs) through the skin of an animal. Such compositions include alcohols, such as ethanol and isopropanol; polyols, such as n-alkanols (C.sub.6 -C.sub.8), limonene, terpenes, dioxolane, propylene glycol, ethylene glycol, other glycols, and glycerol; sulfoxides, such as dimethylsulfoxide ("DMSO") and methyl dodecyl sulfoxide; esters such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl propionate, and capric/caprylic triglycerides; ketones, such as 2-alkyl cyclohexanones, t-butyl cyclohexanones, and various C.sub.8 derivatives; amides, such as acetamides; oleates, such as triolein; various surfactants, such as Brij 96, Tweens (Atlas Chemical Company), myrjs, and sodium lauryl sulfate; various alkanolic acids such as caprylic acid (C.sub.6 -C.sub.10); lactam compounds, such as Azone; alkanols, such as oleyl alcohol; and admixtures thereof. These compositions are believed to enhance permeation of biologically active agents by acting at the lipid matrix of the stratum corneum (i.e. by enhanced intercellular matrix diffusion).

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L77: Entry 24 of 26

File: DWPI

Apr 30, 1997

DERWENT-ACC-NO: 1998-016907

DERWENT-WEEK: 199802

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TITLE: Therapeutic ointment composition - comprises natural plant extracts, useful in, e.g. treatment of wounds and burns

INVENTOR: CARASAVA, M; DOBRESCU, D ; JURAVLE, G ; JURAVLE, V I ; MANZATU, I

PATENT-ASSIGNEE:

ASSIGNEE	CODE
CARASAVA M	CARAI
DOBRESCU D	DOBRI
JURAVLE G	JURAI
JURAVLE V I	JURAI
MANZATU I	MANZI
SC TEHMAN SRL	TEHMN

PRIORITY-DATA: 1992RO-0200246 (March 4, 1992)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
RO 107087 B1	April 30, 1997		000	A61K009/06

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
RO 107087B1	March 4, 1992	1992RO-0200246	

INT-CL (IPC): A61 K 9/06; A61 K 35/78

ABSTRACTED-PUB-NO: RO 107087B

BASIC-ABSTRACT:

Ointment composition comprises: (a) processed conifer resin 5-15%; (b) Hippophae oil 5-20%; (c) bee glue 0.5-6%; (d) soft extract of Gemma populi; (e) soluble collagen 1-5%; (f) oily extract of Calendula, Hyperici and Radix Bardanae 10- 40%; (g) lavender oil 0.5-3%, and (h) structured water A incorporated in ointment base 5-25%. Also claimed is an ointment base comprising: (a) beeswax 5-15%; (b) acetyl alcohol 5-20%, and (c) cholesterol and added benzocaine 0.5-3%.

USE - The ointment has therapeutic properties and it is used in treatment of wounds, varicose ulcers and grade I-IV burns.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: THERAPEUTIC OINTMENT COMPOSITION COMPRISE NATURAL PLANT EXTRACT USEFUL TREAT WOUND BURN

DERWENT-CLASS: B04

CPI-CODES: B01-D02; B04-B01C1; B04-B01C2; B04-N02; B10-B02A; B10-E04D; B12-M02;

WEST

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L75: Entry 4 of 5

File: USPT

Sep 15, 1998

DOCUMENT-IDENTIFIER: US 5807568 A

TITLE: Enhanced delivery of topical compositions containing flurbiprofen

Detailed Description Text (17):

The compositions of the invention may further comprise from about 0 to 10%, preferably from about 0 to 5%, even more preferably from about 0.1 to 2%, penetration enhancing compositions which provide improved transepidermal or percutaneous delivery of flurbiprofen, when compared to other compositions which lack the presence of such penetration enhancing compositions. Such compositions are well known in the art and are described in, for example, World Patent No. 93/17710, the disclosure of which is hereby incorporated by reference. Suitable penetration enhancers include terpenes, terpene alcohols and essential oils. Examples of such penetration enhancers are d-limonene, terpinen-4-ol, menthone, 1,8-cineole, l-pinene, a-terpineol, carveol, carvone, pulegone, piperitone, ascaridole, ylang ylang, anise, chenopodium, eucalyptus, 3-carene, cyclohexene oxide, limonene oxide, a-pinene oxide, cyclopentene oxide, 7-oxabicyclo[2.2.1]-heptane, eucalyptol, peppermint oil and the like. Preferred penetration enhancing compositions are d-limonene in an amount of about 0.5%.